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**RESOLUTION OF AMINO ACIDS THROUGH
THE BROMO-CAMPHOR SULFONAMIDES**

BY

RAYMOND COLONIUS KILLEFER

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THE BROMO-CAMPHOR SULFONAMIDES**

BY

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THESIS

FOR THE

DEGREE OF BACHELOR OF SCIENCE

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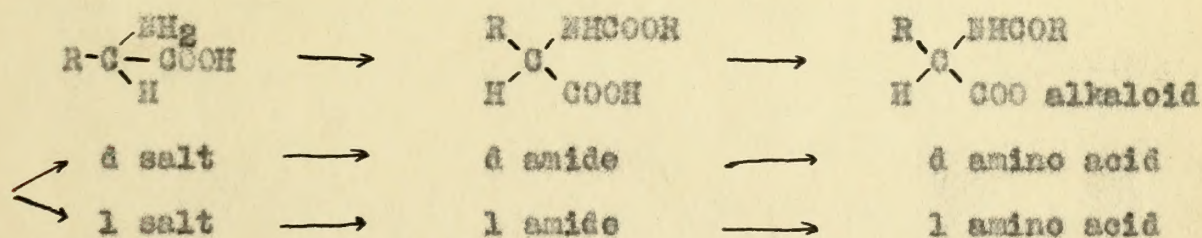
RESOLUTION OF AMINO ACIDS THROUGH THE BROMO-CAMPHOR SULFONAMIDES.

INTRODUCTION

Amino acids contain a carboxyl group and one or more amino groups in direct union with carbon. They are of physiological importance, since many are decomposition products of proteins, and some are natural products. Many of them contain an asymmetric carbon atom and exist, therefore, in three isomeric modifications, the dextro, the laevo, and the racemic.

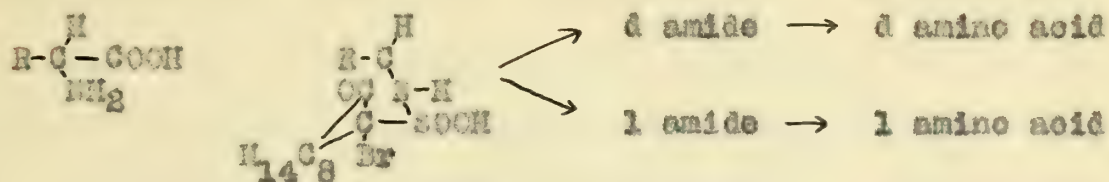
The amino acids prepared synthetically in the laboratory are racemic, while those in the body occur in the active dextro or laevo form. In order to study their physiological action in the body, the racemic form must be resolved into its active forms.

This is usually done by Fisher's method of resolution. It consists of covering up the amino group with an acyl groups such as R C O, forming a salt of this amide, then separating the dextro and laevo forms of the amide, hydrolyzing off the R C O group to get back the free amino group. It may be represented graphically as follows:



It was thought that by combining the amino acid with an acid that contained an asymmetric carbon atom, it would be possible to obtain crystalline amides which could be used for the resolution of the amino acid, thus avoiding a number of steps in Fisher's method. Bromo-camphor sulfonic acid was chosen for the prepara-

tion of the amides from the amino acids, as it has often been used in working with optically active bases. A graphical outline of the method would be:



HISTORICAL AND THEORETICAL PART

Several amino acids were prepared and a study of the reaction and best conditions of preparation was made.

α -amino-caprylic acid which was selected for resolution, was prepared first. This acid has been prepared in 35% yields by treating the ammonium addition compound of heptaldehyde with aqueous hydrocyanic acid followed by hydrolysis.¹ It has been prepared in larger yields (45%) by treating the heptaldehyde with ammonium chloride and sodium cyanide and subsequent hydrolysis of the nitrite group.² This latter method was the one used in this work, and the same yields were obtained. An attempt was made to increase the yield by use of mechanically stirring in the preparation of the amino cyanide, and by lengthening the time of hydrolysis. It was not possible, however, to increase the yield.

Glycocoll was next prepared. The usual method is that of Kraut's, in which chloroacetic acid is treated with ammonia, and the glycocoll resulting purified by crystallizing as the copper salt.³ The method used in this work was that of treating chloroacetic acid with ammonia in the usual way, and then removing the ammonium chloride by means of lead oxide. The lead oxide reacts with ammonium chloride to form insoluble lead chloride, and ammonia, which is boiled off. It was found necessary to filter off the lead chloride, and treat with lead oxide again, in order to remove all the ammonium salts. A large amount of lead oxide was necessary as a soluble lead salt of glycocoll is formed. In order to remove this lead from the solution, it was found necessary to precipitate the lead with hydrogen sulfide under pressure. A large bulky precipitate is obtained, which is quite difficult to

handle. The glycoceoll obtained by this method is a fairly pure compound, but has a sour taste. A test was made to see if it were due to hydrochloric acid, but not chlorides were formed.

α -amino-methyl-ethyl-acetic acid has been prepared by treating the cyanhydrin addition product of methyl-ethyl ketone with ammonia, followed by hydrolysis and purification from ammonium salts by means of lead oxide.⁴ It was prepared in this work by treating methyl-ethyl ketone with ammonium chloride and sodium cyanide followed by hydrolysis of the nitrile groups, and purification by means of lead oxide. A fairly pure product was obtained in 45% yields.

Bromo-campher sulfonic acid has been prepared by treating bromo-campher with anhydrosulfuric acid.⁵ A newer method, using chlorosulfuric acid, as developed by Kipping and Pope, can be used.⁶ This latter method was used with fairly good results. However, in every case, our yields were only about two thirds of those given in the literature.

It was necessary to prepare bromo-campher. Armstrong's and Mathew's method was used.⁷ A pure product was obtained, though in only about two thirds the yield given in the literature.

Bromo-campher sulfonamide of α -amino-caprylic acid was prepared by the usual method of condensing an amino acid with a sulfonic acid chloride in the presence of sodium hydroxide. An amide was formed, but instead of being a crystalline solid, it was found to be a sticky substance which could not be crystallized. An attempt was made to prepare sulfonamides of phenylamino-acetic acid, and other amino acids, but in every case it was found that these amides were sticky, oily substances. It was therefore con-

cluded that it was the nature of the bromo-camphor sulfon derivatives of amino acids to be sticky and uncrystallizable. As a result, it was impossible to continue from this point with the work of resolution.

EXPERIMENTAL

α -amino-caprylic Acid.

Fifty-five grams of sodium cyanide was dissolved in 100 cc. of water and to the solution 57 grams of ammonium chloride was added. To this solution was added a solution of 114 grams of heptaldehyde in 100 cc. of methyl alcohol. The solution became warm and after about a half hour, a layer of the amino cyanide was taken up in ether, and the ether distilled off. To accomplish the hydrolysis, 500 cc. of HCl (350 cc. of acid, sp. gr. 1.19 and 150 cc. of water) was added and the solution refluxed for six hours. It was cooled and filtered to remove most of the oily impurity which had separated. The amino acid was precipitated from the filtrate by adding ammonium hydroxide. The product obtained was quite dark in color. For purification, it was dissolved in dilute NaOH solution (10-15%) and boiled with bone-black. The solution was filtered and the amino acid precipitated by means of a saturated solution of ammonium chloride. The product was filtered with suction and washed with water and dried on filter paper. The yield was 70-75 grams (43-47% of the calculated amount.)

Glycocoll.

Ninety-five grams of chloroacetic acid was dissolved in 1200cc. of ammonia water (sp. gr. .90) and 95 cc. of water added in a large flask. The solution was shaken well and allowed to stand for twenty-four hours. The glycocoll solution was poured into a large evaporating dish and boiled until the excess ammonia was driven off. To accomplish the removal of the ammonium chloride, the glycocoll solution was diluted with water to 900 cc. and 200 grams of lead

oxide added. The mixture was rapidly boiled to a small volume on the hot plates and then heated on a steam cone until most of the water had been driven off. The mixture of lead chloride and glyccoll was taken up in 900 cc. of water and the lead chloride filtered off. The filtrate was treated again with 250 grams of lead oxide, boiled on a hot plate, and finally heated on a steam cone to drive off the last traces of ammonia. The mixture was taken up in 400 cc. of water and the lead chloride filtered off with suction. The lead in the filtrate was precipitated as lead sulfide with hydrogen sulfide under pressure, and then filtered. The filtrate was evaporated until a fairly concentrated solution of glyccoll was obtained, and then a large volume of 95% alcohol was added. The crystallized glyccoll was filtered off with suction, washed with a little 95% alcohol and dried on filter paper. The yield was 30-34 grams (40-45% of the calculated amount).

α -amino-methyl-ethyl-acetic Acid.

Fifty-five grams of sodium cyanide was dissolved in 100 cc. of water and to the solution 54 grams of ammonium chloride was added. To this solution was then added 72 grams of ethyl-methyl ketone. The solution became warm and a layer of the amino cyanide began to separate after an hour. The reaction mixture was allowed to stand for twenty-four hours. The amino cyanide was taken up in ether and the ether distilled off. To accomplish the hydrolysis 300 cc. of hydrochloric acid (sp. gr. 1.19) was added, and the solution refluxed for six hours. The solution was then evaporated to dryness in a large evaporating dish to remove any impurities. To remove the ammonium salts, 250 grams of lead oxide was added to the solution, which was boiled to drive off the

ammonia. The solution was boiled down to a small volume on the hot plate and heated on the steam cone to dryness. The residue was taken up in 900 cc. of water, and the lead chloride filtered off. The filtrate was once more treated with lead oxide, and the boiling and evaporation carried out to remove all the ammonium salts. The residue was taken up in 400 cc. of water, and the lead chloride filtered off with suction. The lead remaining in the solution was precipitated with hydrogen sulfide under pressure, and the lead sulfide filtered off. The filtrate was evaporated to dryness on the steam cone. The amino-methyl-ethyl-acetic acid remained as a residue. The yield was 51-54 grams (43-46% of the calculated amount).

Bromo-campher sulfonic Acid Chloride.

One hundred grams of bromo-campher was dissolved in 200 grams of chloroform. To this solution 75 grams of freshly distilled chlorosulfonic acid was added, and the mixture heated on the steam cone for twelve hours. It was then cooled, poured into water and the chloroform layer separated. The aqueous solution was neutralized with calcium carbonate, and the calcium sulfate formed filtered off with suction. To the filtrate, which was heated nearly to boiling, 45 grams of ammonium carbonate was added. Calcium carbonate was precipitated which was filtered off. The filtrate was evaporated until the ammonium salt of the bromo-sulfur sulfonic acid began to crystallize out. It was allowed to cool, and the ammonium salt filtered off by suction. The product was of a brown color. It was not purified further though it may be by washing with methyl alcohol, and then recrystallizing from boiling water. The yield was 78-81 grams (65-67% of calculated).

Bromo-campher.

One hundred and fifty grams of powdered campher was placed in a large flask and heated on a water bath. To it 160 grams of bromine was added very slowly with constant stirring. The mixture was poured into a large volume of cold water. The bromo-campher which separated was filtered off by suction, and washed with water. It was crystallized twice from boiling methyl alcohol. A pure product was obtained which melted at 74 C. The yield was 122-125 grams (52-54% of the calculated amount).

Bromo-campher sulfonamide of α -amino-caprylic acid.

Sixteen grams of α -amino-caprylic acid was dissolved in 25 cc. of water containing 4 grams of sodium hydroxide. Thirty-two grams of bromo-campher sulfonic chloride was added, and the mixture mechanically stirred. Four grams of sodium hydroxide in 10 cc. of water was gradually added within the next half hour. After stirring for four hours the solution was acidified with hydrochloric acid. The product obtained was a sticky mass that could not be crystallized from any of the common solvents. A qualitative test was made showing the presence of nitrogen and sulfur, thus indicating that the amide was formed. An attempt was made to prepare the sulfon amides of phenyl-amino-acetic acid and other amino acids, but in every case it was found that these amides were sticky, oily substances. It was therefore concluded, that it was the nature of the bromo-campher sulfon derivatives of amino acids to be sticky and uncrystallizable.

SUMMARY

1. α -amino-caprylic acid was prepared in 43-47% yields as a fairly pure product.
2. Glycosell was obtained in 40-48% yields by purifying from ammonium salts by means of lead oxide. It has a sour taste which is due to some impurity.
3. Methyl-ethyl-amino-acetic acid was prepared in 45% yields as a pure product. Lead oxide was used to remove the ammonium salt.
4. Bromo-camphor sulfinic acid chloride and bromo-camphor were prepared in yields equal to about two thirds of those given in the literature.
5. The bromo-camphor sulfenamide of α -amino-caprylic acid was prepared, and was found to be a sticky product which could not be crystallized from any common solvents. Several other amino acids were tried among them being phenylamino-acetic acid, and the same kinds of sticky products were obtained. It was, therefore, concluded that it was the nature of the bromo-camphor sulfon derivatives of amino acids to be sticky and uncrystallizable.



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